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DESIGN AND DEVELOPMENT OF SINGLE CORE OSMOTIC PUMP (SCOP) FOR POORLY SOLUBLE DRUG

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ABSTRACT

The present work aims towards the design and development of controlled release formulation of poorly soluble drug Carbamazepine (CBZ) based on osmotic technology by using single core osmotic pump (SCOP) approach. Carbamazepine (CBZ) is a first-line antiepileptic drug (AED) drug used for the treatment of partial and tonic-clonic seizures. The concentrations of Natrosol 250L (rate controlling polymer) and Sodium chloride (Osmogen) added to the core tablet were optimized. Cellulose acetate (CA) and Polyethylene glycol (PEG 8000) were used as semipermeable membrane and pore former, respectively. The effect of different formulation variables namely concentration of rate controlling polymer and osmogen in the core tablet, % pore former, % weight gain, orifice diameter, pH of the dissolution medium and agitation intensity on the *in vitro* release was studied. CBZ release was directly proportional to % of Osmogen and inversely proportional to % of rate controlling polymer in core tablet. The system was found to deliver CBZ at a zero order rate for 24 h independent of pH and agitation intensity can be useful as improved AEDs efficacy, tolerability and patient compliance.

KEYWORDS: SCOP**,** Natrosol 250L, Cellulose acetate, Osmogen, PEG 8000.

INTRODUCTION

The novel drug delivery systems are gaining popularity over conventional drug delivery because of its many add-on features. The conventional dosage form results in constantly changing, unpredictable and often sub-therapeutic plasma concentrations, leading to marked side effects in some cases. Conventional oral drug delivery system releases the drug immediately and does not release the drug in a controlled manner and effective concentration at target site which leads to major drawback of fluctuating drug levels. Better therapy management demands for controlled or modified release drug delivery systems. The osmotic drug delivery is a very promising approach which utilizes the principle of osmotic pressure for controlled delivery of drugs. The system embraces simple and ease of formulation, improved patient compliance, reduced dosing frequency and prolong therapeutic effect with uniform blood concentration.[1,3] The osmotic systems form a major segment of drug delivery products because of their advantages and strong market potential.[4,5]

Epilepsy is a chronic disorder in which nerve cell activity in the brain is disturbed, causing seizures or periods of unusual behavior, sensations and sometimes loss of consciousness demands better management since it can be dangerous during activities such as driving or swimming. The drug Carbamazepine (CBZ), a first-line antiepileptic drug (AED) is promising for the treatment of partial and tonic-clonic seizures.[6] CBZ belongs to class II of BCS classification having low solubility and high permeability.[7] It is well absorbed from gastrointestinal tract possessing bioavailability upto 80% and 76% protein binding and is metabolized in liver by CYP3A4 to active epoxide form (10-11 epoxy Carbamazepine). CBZ is a narrow therapeutic index drug with initially its plasma half life is 20-40 hours but, decreases to 10-15 hours on chronic medication due to auto-induction of metabolism. Serum carbamazepine levels fluctuate considerably, even with multiple daily doses[8,9] and can be associated with transient adverse effects at peak concentrations. In patients receiving polytherapy, it is of great clinical importance to assure a steady level of CBZ during 24 hour carbamazepine therapy. The literature envisaged reveals the need for the development of controlled-release formulations of AEDs to overcome the fluctuations in serum drug levels as associated with conventional drug delivery systems for improved anti-epileptic therapy.[10,13]
The conversion of CBZ to Carbamazepine dihydrate (CBD) in the gastrointestinal tract is one of the major rate-limiting steps in bioavailability of oral dosage forms. Dihydrate of CBZ has one-third solubility as compared to its anhydrous form. The burst release of CBZ from immediate release (IR) dosage forms lead to super-saturation of the drug in GIT and

facilitates the formation of CBD resulting in poor dissolution rate and bioavailability. Another approach to address the issue is the formulation of controlled release dosage forms that would prevent the burst release, super-saturation, and CBD formation. The prevention of the formation of CBD crystals is of great importance since the crystals dissolve slowly and may lead to unpredictability in bioavailability profile. The controlled release formulations of CBZ can be useful as AEDs with improved efficacy, tolerability and patient compliance in comparison to immediate-release formulations.[14,17]

Single core osmotic pumps (SCOP) are reliable system for delivery of low solubility drug and a suitable dosage form for oral drug delivery. The SCOP comprises of a single layer of osmotic core with the drug, surrounded by a semi-permeable membrane. This membrane consist of an orifice through which drug is delivered. The dosage form when in contact with aqueous fluids, imbibes water at a rate determined by the fluid permeability of the membrane and osmotic pressure of the core formulation. The rate of imbibitions of water is determined by the fluid permeability of the membrane and the osmotic pressure of the compressed tablet. This osmotic imbibition of water results in the formation of a saturated solution of drug within the core, which is released at controlled rate through the delivery orifice. The tablets formulated using poorly soluble drugs devoid of polymers results in settling of drug particles in the core and poor drug delivery unless the tablet is constantly agitated to prevent the drug particles from settling. The rate of settling is enhanced in case of large drug particles with high density. The use of hydrophilic polymers may circumvent the issue and prevent the settling of the drug particles before they exit through the delivery orifice.[18,23]

Drug release from these systems is independent of pH and other physiological parameters. Zero order release characteristics could be achieved by optimizing the parameters of the delivery system.

MATERIALS AND METHODS

Materials

Carbamazepine was procured as a gift sample from Swapnroop Drugs and Pharmaceutical, Aurangabad, India. The excipients was received as a gift samples, Hydroxyethyl cellulose (NATROSOL 250L) - DKSH India Pvt. Ltd. Mumbai, Cellulose acetate (CA-398-10NF) - Signet Pharma, Mumbai, India. The Sodium lauryl sulfate (KOLLIPHOR® SLS Fine) - BASF India, Mumbai, Sodium chloride, Lactose anhydrous, Polyvinyl pyrrolidone (PVP

K30), Polyethylene glycol (PEG 8000) and Magnesium stearates - Shreya Life Sciences Pvt. Ltd., Aurangabad, India. All other chemicals used were of analytical grade.

Drug Analysis

CBZ was analyzed by double-beam UV–visible spectrophotometer (Shimadzu 1700 Pharm Spec) at λ max 284 nm. Calibration curves were prepared in deionized water, pH 1.2, phosphate buffer 6.8 and phosphate buffer 7.4 in the concentration range of 4–20 µg/ml. No enzymes were added to pH 1.2, phosphate buffer 6.8 and phosphate buffer 7.4.[24]

Drug‑Excipients Compatibility Study

The drug‑excipients compatibility study was done by differential scanning calorimetry (DSC), using a SHIMADZU DSC‑60 differential scanning calorimeter. The system was calibrated with a high purity sample of Indium. The DSC thermograms were scanned at the heating rate of 20°C/min over a temperature range of 70‑300°C. Peak transitions and enthalpy of fusion were determined for the samples using TA60 integration software. The DSC analysis shows no change in endothermic peak of CBZ. The study indicated that there was no drug-excipient incompatibility/interaction (Fig. 1 and 2).

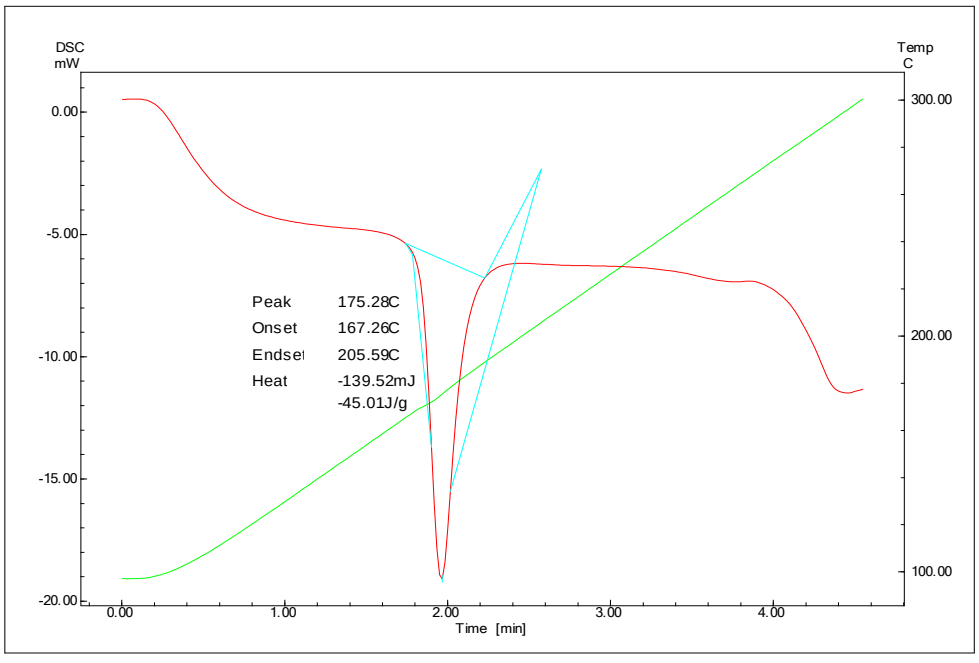

Fig. 1: DSC thermogram of Carbamazepine.

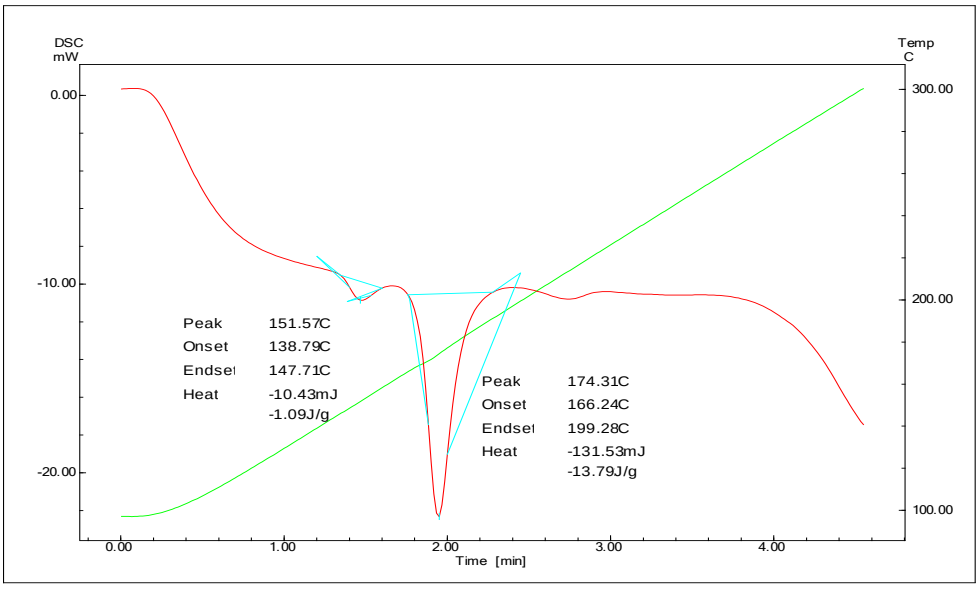

Fig. 2: DSC thermogram of Carbamazepine with other excipients (Lubricated blend).

Design and Development of Single Core Osmotic Pump (SCOP) Tablet

The tablets were prepared by wet granulation technique. The ingredients were weighed accurately as per the formula depicted in the Table.13. The weighed quantity of ingredients was blended for 15-20 min and granulated with water. The wet mass was passed through sieve no. 20. The resultant granules were dried in hot air oven at 60 ± 5°C to get loss on drying (LOD) not more than 2.5% w/w. The dried granules were lubricated and core tablets were compressed at an average weight of 350 mg using 9.50 mm concave punches plain on both side and 7.0-9.0 kg/cm^2 hardness on 12 station rotary tablet machine (Labpress, Cip Machinery Ltd.).

The core tablets were coated with solution of acetone: water containing cellulose acetate along with pore former i.e. PEG 8000 to get a weight gain of 7% w/w using R & D pan coater (Ideal Cuers Ltd.) having pan with 3 baffles, pan speed 20-25 rpm, pump speed 1rpm, inlet temperature 45˚C, air flow 1 kg/cm², spray nozzle diameter 1 mm, Air gun distance from tablet bed being 10 cm. The coated tablets were mechanically drilled on one side with 0.6 mm drill.

***In vitro* Drug Release Study**

The drilled tablets were subjected to an *in vitro* drug release study as per USP Dissolution Test. The dissolution study was performed using the USP Apparatus 1 (Basket) in 900 ml of deionized water for 24 h at 100 rpm and 37 ± 0.5ºC. Aliquots of 5 ml were withdrawn at an

interval of 1, 2, 3, 4, 6, 8, 9, 10, 12, 16, 20 and 24 h. The withdrawn samples were replaced with fresh dissolution medium. The samples were filtered through Whatman filter paper and analyzed by double-beam UV–visible spectrophotometer (Shimadzu 1700 Pharm Spec) at λ max 284 nm.

The Effect of Formulation Variables on Drug Release

The formulated tablets were evaluated to study the effects of variables such as the amount of rate controlling polymer and osmogen in the core tablet, concentration of pore former and %weight gain by coating, orifice diameter, pH of the dissolution medium and agitation intensity on drug release.

RESULTS AND DISCUSSION

Solubility Enhancement of CBZ by PVP K30 and Sodium Lauryl Sulfate (SLS) Physical Mixtures (PMs)

In the present study PVP K30 and SLS were added to the core tablet to enhance the solubility of CBZ in an aqueous medium.[25,26] (Table 1)

Table 1: Solubility of CBZ in various CBZ-PMs

Physical Mixture	Code	Ratio	Solubility (mg/mL)
Pure CBZ	CBZ	1	0.229
CBZ/PVP K30	PM1	1:0.25	0.301
CBZ/PVP K30/SLS	PM2	1:0.20:0.010	0.411
CBZ/PVP K30/SLS	PM3	1:0.15:0.015	0.522

Results revealed that, SLS in combination with PVP K30 improves the wettability and contributes to solubility enhancement of CBZ. Therefore, through the combining effects of solubility enhancement of both PVP K30 and SLS adding small amounts to tablet core can improve release pattern. PM3 is used for the optimization of tablet core formulation.

Selection of Rate Controlling Polymer

In the present study for the selection of hydrophillic rate controlling polymer in the core tablet, preliminary batches were prepared using 10% w/w of core weight of Hydroxyethyl cellulose (Natrosol 250L), Hydroxy propyl methyl cellulose (Methocel K4M), Sodium carboxymethyl cellulose (Sodium CMC) and Xanthan Gum (Xantural 75).

The concentration of drug, osmogen, other excipients in the core tablet, coating composition and orifice diameter was kept constant (Table 2). The tablets were evaluated for release study

for 24 h in 900 ml dissolution medium (deionized water) using USP Apparatus 1 (Basket) with 100 rpm.

Table 2: Selection of hydrophilic rate controlling polymer.

Ingredients	Weight (mg)			
	E1	E2	E3	E4
Intragranular Composition				
Carbamazepine	200.00	200.00	200.00	200.00
Hydroxy propyl methyl cellulose (Methocel K4M)	35.00	-	-	-
Hydroxyethyl cellulose (Natrosol 250L)	-	35.00	-	-
Sodium carboxymethyl cellulose	-	-	35.00	-
Xanthan Gum (Xantural 75)	-	-	-	35.00
Sodium chloride	50.00	50.00	50.00	50.00
Lactose anhydrous	62.00	27.00	27.00	27.00
Polyvinylpyrrolidone (Kollidon 30)	30.00	30.00	30.00	30.00
Sodium lauryl sulfate	3.00	3.00	3.00	3.00
Purified water	q.s.	q.s.	q.s.	q.s.
Magnesium stearate	5.00	5.00	5.00	5.00
Core Tablet Weight	350.00	350.00	350.00	350.00
Extended Release Coating Composition				
Cellulose acetate 398-10	23.27	23.27	23.27	23.27
Polyethylene glycol (PEG 8000)	1.23	1.23	1.23	1.23
Acetone	q.s	q.s	q.s	q.s
Water	q.s	q.s	q.s	q.s
Coated Tablet Weight	374.50	374.50	374.50	374.50

The selected polymers were evaluated for their effectiveness for delivering a poorly water soluble CBZ from SCOP for parameters lag time (T_L) and Q_3, Q_6, Q_{12}, Q_{24} (% drug release after 3h, 6h, 12h, and 24h, respectively).

The results revealed that the lag time for formulations containing Methocel K4M (E1), Sodium CMC (E3) and Xantural 75 (E4) was 3h, 2h and 2h respectively. The shortest lag time (T_L: 1 h) and drug release for Q_3, Q_6, Q_{12} and Q_{24} from the formulation E2 comprising of Hydroxyethyl cellulose (Natrosol 250L) as a hydrophilic rate controlling polymer showed promising release for a period of 24h and was selected for further studies. The Q_3, Q_6, Q_{12} and Q_{24} for formulation containing Natrosol 250L (E2) were 8.12%, 27.43%, 55.33% and 72.41%, respectively (Table 3) (Fig. 3)

Table 3: Comparative parameters for selection of hydrophilic rate controlling polymer.

Parameter	Formulation Code			
	E1 (Methocel K4M)	E2 (Natrosol 250L)	E3 (Sodium CMC)	E4 (Xantural 75)
T_L (h)	3.00	1.00	2.00	2.00
Q_3 (%)	0.00	8.12	4.96	1.18
Q_6 (%)	4.93	27.43	19.75	9.10
Q_{12} (%)	21.98	55.33	41.66	28.54
Q_{24} (%)	31.75	72.41	54.00	48.03

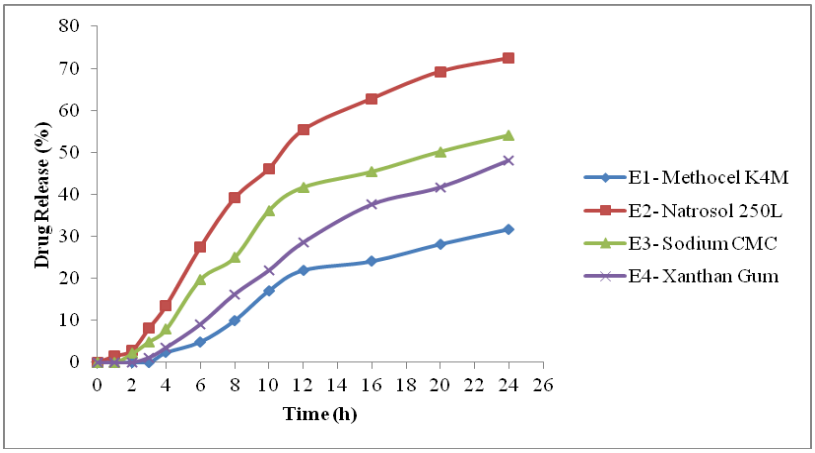

Fig. 3: Release profiles of formulations E1-E4 for selection of hydrophilic rate controlling polymer.

Hydroxyethyl cellulose (Natrosol 250L) with drug particles forms a viscous suspension in water and expels the contents through the orifice with a relatively low force. The effectiveness of HEC is possibly related to its rheological properties, rate of hydration and the pressure produced during swelling maintained the integrity of the system for as period of 24 h. The uniform rate of swelling of the polymer ensured the drug is release at a relatively constant rate.

Effect of Concentration of Pore Former on Drug Release and Coat Consistency

To investigate the effect of concentration of pore former on drug release and coat consistency, the core tablets of formulation E2 were coated with varying concentration of pore former PEG 8000 and solid content, % weight gain and orifice diameter was kept constant (Table 4).

Table 4: Coating compositions to study effect of concentration pore former on drug release.

Ingredients	Formulation Code		
	E2A	E2B	E2C
Cellulose Acetate 398-10 (%)	3.80	3.60	3.40
PEG 8000 (%)	0.20	0.40	0.60
Acetone (w/w)	q.s.	q.s.	q.s.
Purified water (w/w)	q.s.	q.s.	q.s.
Parameter			
CA : PEG 8000	95:05	90:10	85:15
Solid content (%)	4.00	4.00	4.00
Weight gain (%)	7.00	7.00	7.00
Orifice Diameter (mm)	0.6	0.6	0.6

The drug release increased with an increase in the level of PEG 8000 (Fig. 4). This could be accounted to an increased hydrohilicity of semi-permeable membrane and rate of water penetration across the membrane. The formulation E2B comprising of CA: PEG in the ratio of 90:10 resulted in a good hydrophilic/lipophilic balance in semi-permeable structure and drug release profile with zero order kinetic (Table 5).

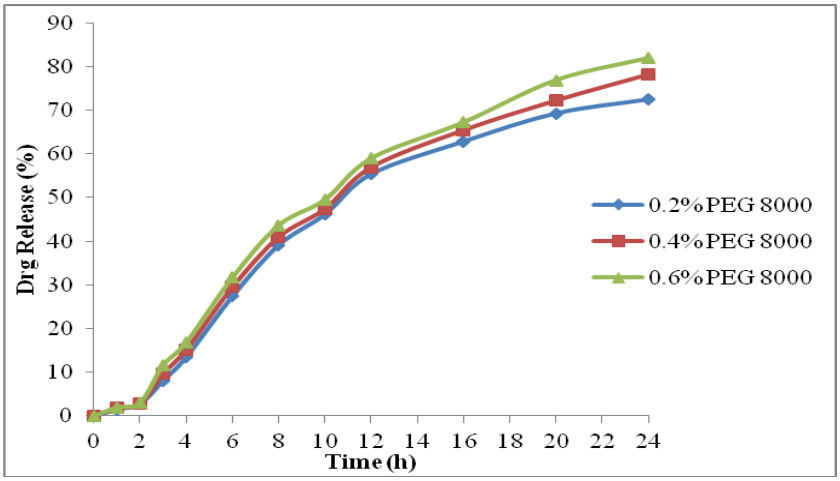

Fig. 4: Effect of concentration of pore former on drug release.

Table 5: Effect of concentration of pore former on coat consistency.

Parameter	Formulation Code		
	E2A	E2B	E2C
CA:PEG 8000	95:05	90:10	85:15
Coat Consistency	+++	+++	++

+++: No change, ++: Swell

Effect of % Weight Gain on Drug Release and Coat Consistency

To investigate the effect of weight gain on drug release and coat consistency, the core tablets of formulation E2 were coated to achieve a weight gain of 5% w/w, 6% w/w, 7% w/w and 8% w/w, respectively, whilst the solid content, CA:PEG ratio of 90:10 was kept constant (Table 6).

Table 6: Coating compositions to study effect of % weight gain on drug release.

Ingredients		Formulation Code		
	E2B1	E2B2	E2B3	E2B4
Cellulose Acetate 398-10 (%)	3.60	3.60	3.60	3.60
PEG 8000 (%)	0.40	0.40	0.40	0.40
Acetone (w/w)	q.s.	q.s.	q.s.	q.s.
Purified water (w/w)	q.s.	q.s.	q.s.	q.s.
Parameter				
Weight gain (%)	5.00	6.00	7.00	8.00
Solid content (%)	4.00	4.00	4.00	4.00
CA:PEG 8000	90:10	90:10	90:10	90:10
Orifice Diameter (mm)	0.6	0.6	0.6	0.6

The results revealed that with an increase in the %weight gain the consistency of coat improved (Table 7) but the drug release decreased (Fig. 5). The increase in the %weight gain resulted in an increase in the resistance of the membrane to water diffusion but the rate of imbibing water decreased leading to decrease in liquefaction rate of the tablet core and drug release. The formulation E2B3 with 7% weight gain was further selected for the development of SCOP with a desired consistency for a period of 24 h.

Table 7: Effect of % weight gain on coat consistency.

Parameter	Formulation Code			
	E2B1	E2B2	E2B3	E2B4
Weight Gain (%)	5.00	6.00	7.00	8.00
Coat Consistency	+	++	+++	+++

+++: No change, ++: Swell, +: Burst

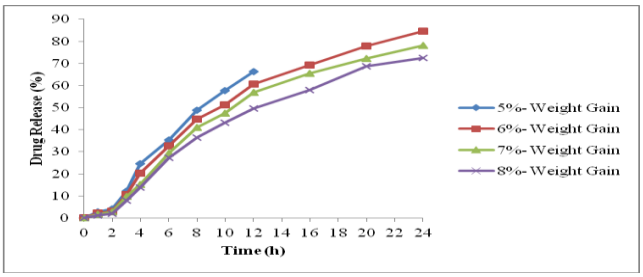

Fig. 5: Effect of % weight gain on drug release.

Effect of Various Concentrations of Rate Controlling Polymer and Osmogen in Core Tablet on Drug Release

To study the effect of various concentrations of rate controlling polymer and osmogen in core tablet on drug release a 3^2 factorial design of experiment was constructed where concentration of hydrophillic rate controlling polymer Hydroxyethyl cellulose i.e. Natrosol 250L (%) and osmogen i.e. sodium chloride (%) in core tablet were selected as the factors. All other formulation and processing variables were kept constant throughout the study (Table 8).

Table 8: Formulation of factorial design formulations.

Ingredients (mg)	**Formulations**								
Core Tablet	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Carbamazepine	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0
Hydroxy ethyl cellulose	**21.00**	**21.00**	**21.00**	**28.00**	**28.00**	**28.00**	**35.00**	**35.00**	**35.00**
Sodium chloride	**49.00**	**56.00**	**63.00**	**49.00**	**56.00**	**63.00**	**49.00**	**56.00**	**63.00**
Lactose anhydrous	42.00	35.00	28.00	35.00	28.00	21.00	28.00	21.00	14.00
Polyvinylpyrrolidone	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00
Sodium lauryl sulfate	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s
Magnesium stearate	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Core tablet weight (mg)	350.0	350.0	350.0	350.0	350.0	350.0	350.0	350.0	350.0
Extended release coating									
Cellulose acetate 398-10	22.05	22.05	22.05	22.05	22.05	22.05	22.05	22.05	22.05
PEG 8000	2.45	2.45	2.45	2.45	2.45	2.45	2.45	2.45	2.45
Acetone	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total weight (mg)	374.5	374.5	374.5	374.5	374.5	374.5	374.5	374.5	374.5
Drilling									
Orifice Diameter (mm)	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60

Dissolution Studies

Factorial design batches of SCOP were subjected to *in vitro* drug release studies in 900 mL deionized water using USP Apparatus 1 (Basket) at 100 rpm for 24 h. Fig. 6 summarizes the dissolution profiles of factorial design batches. From the dissolution profiles it is evident that an increase in % of osmogen (sodium chloride) resulted in an increase in the drug release (Fig. 7). The increase in % of rate controlling polymer (Natrosol 250L) in the core tablet showed decrease in drug release (Fig. 8). The formulation F6 meets USP Dissolution Test acceptance criteria.[27]

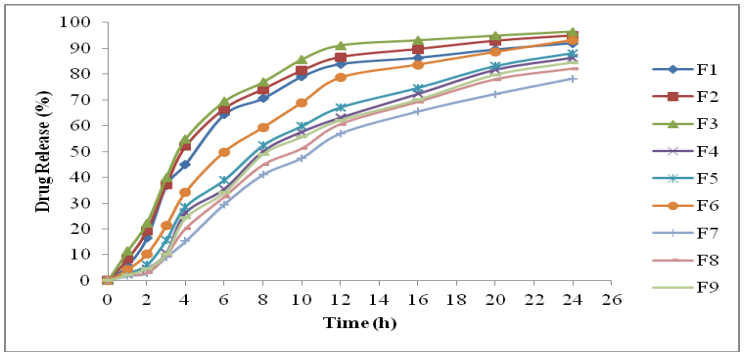

Fig. 6: Dissolution profiles of factorial design batches (F1-F9).

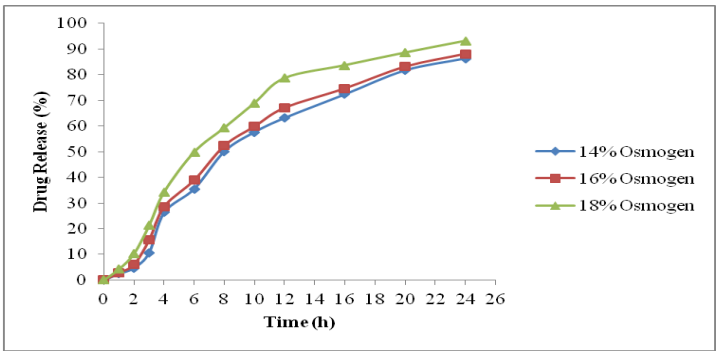

Fig. 7: Effect of % of osmogen on drug release.

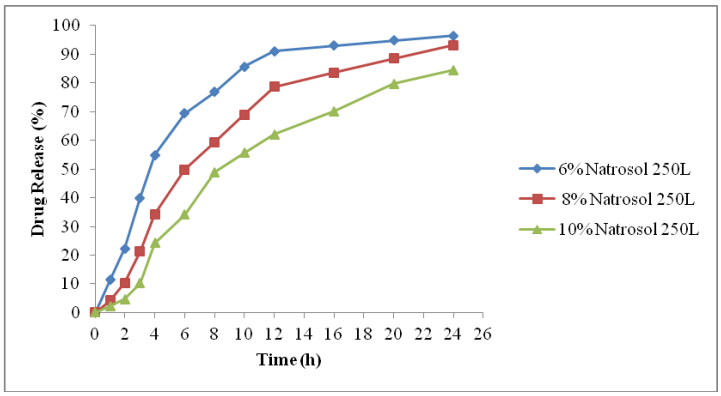

Fig. 8: Effect of % of rate controlling polymer on drug release

Analysis of Data by Design Expert Software

The 3^2 factorial design was selected to study the effect of independent variables % of Natrosol 250L (X_1), % of Sodium chloride (X_2) in core tableton dependent variables Q_3, Q_6, Q_{12} and Q_{24}. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses.

$$Y=b_0+b_1X_1+b_2X_2+b_{12}X_1X_2+b_{11}X_1^2+b_{22}X_2^2$$

Where, Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs and b_i(b_1,b_2,,b_{12},b_{11} and b_{22}) is the estimated coefficient for the corresponding factor X_i (X_1,X_2,X_{12},X_{11},and X_{22}), which represents the average results of changing one factor at a time from its low to high value. The interaction term (X_1X_2) depicts the changes in the response when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. The Q_3, Q_6, Q_{12} and Q_{24} for the nine formulations of design showed a wide variation. The responses of the formulations prepared by 3^2 factorial designs were observed. The responses clearly indicated that the Q_3, Q_6, Q_{12} and Q_{24} values are strongly dependent on the selected independent variables. The fitted regression equations relating the responses Q_3, Q_6, Q_{12} and Q_{24} are shown in the following equations, respectively.

Final Equations in Terms of Coded Factors:

$Q_3 = 15.56 – 14.09\ X_1 + 2.48\ X_2 – 0.52\ X_1X_2 + 7.99\ X_1^2 + 0.42\ X_2^2$

Final equations in Terms of Actual Factors:

Q_3 =15.5644 – 14.0916*Natrosol 250L +2.4800*Sodium chloride – 0.5175*Natrosol 250L*Sodium chloride + 7.9883 *Natrosol 250L^2 + 0.4233 *Sodium chloride^2

(r^2=0.9822)

Final Equations in Terms of Coded Factors:

$Q_6 = 40.76 – 17.35\ X_1 + 3.99\ X_2 – 0.12\ X_1X_2 + 7.95\ X_1^2 + 1.07\ X_2^2$

Final equations in Terms of Actual Factors:

Q6 = 40.7600–17.3533*Natrosol 250L +3.9900*Sodium chloride – 0.1150*Natrosol 250L*Sodium chloride + 7.9500 *Natrosol 250L^2 + 1.0700 *Sodium chloride^2

(r^2=0.9818)

Final Equations in Terms of Coded Factors:

$Q_{12} = 68.84 – 13.63\ X_1 + 4.65\ X_2 – 0.51\ X_1X_2 + 3.90\ X_1^2 + 1.20\ X_2^2$

Final equations in Terms of Actual Factors:

Q_{12}= 68.8366– 13.6266*Natrosol 250L +4.6500*Sodium chloride – 0.5100*Natrosol 250L*Sodium chloride + 3.9000 *Natrosol 250L^2 + 1.2000 *Sodium chloride^2

(r^2=0.9718)

Final Equations in Terms of Coded Factors:

$Q_{24} = 89.15 – 6.42\ X_1 + 2.94\ X_2 + 0.48\ X_1X_2 - 1.15\ X_1^2 + 0.058\ X_2^2$

Final equations in Terms of Actual Factors:

Q_{24}= 89.1477– 6.4183*Natrosol 250L +2.9350*Sodium chloride + 0.4825*Natrosol 250L*Sodium chloride – 1.1516 *Natrosol 250L^2 + 0.0583 *Sodium chloride^2

(r^2=0.9901)

The regression coefficient values are the estimates of the model fitting. The r^2 was high indicating the adequate fitting of the quadratic model. The polynomial equations can also be used to draw conclusions considering the magnitude of co-efficient and the mathematical sign it carries; i.e. positive or negative.

The first variable X_1 (% of Natrosol 250L) in core tablet showed negative coefficient in case of responses $Q_{3,}$ $Q_{6,}$ Q_{12} and Q_{24} i.e. increase in % of Natrosol 250L resulted in the decrease drug release. The second variable X_2 (% Sodium chloride) showed positive coefficient for responses $Q_{3,}$ $Q_{6,}$ Q_{12} and Q_{24} i.e. increase in % of Sodium chloride resulted in the increase in the drug release.

ANOVA Study

The evaluation and interpretation of research findings are important and the significance of p-value is valuable in research findings. The coefficients of X_1 and X_2 were found to be significant at $p<0.05$, hence confirmed the significant effect of both the variables on the selected responses. Overall both the variables caused significant change in the responses. ANOVA and Multiple regression analysis were done using Stat-Ease Design Expert 7.1.4 software.

Response Surface Plots

The response surface plots were generated using Design Expert 7.1.4 software (Fig. 9-12) to observe the effect of independent variables on the response studied such as $Q_{3,}$ $Q_{6,}$ Q_{12} and Q_{24} respectively. The response surface plots revealed that the various combinations of independent variables X_1 and X_2 may satisfy any specific requirement (i.e. maximum drug release upto 24 h) while taking into consideration various factors involved in dosage form.

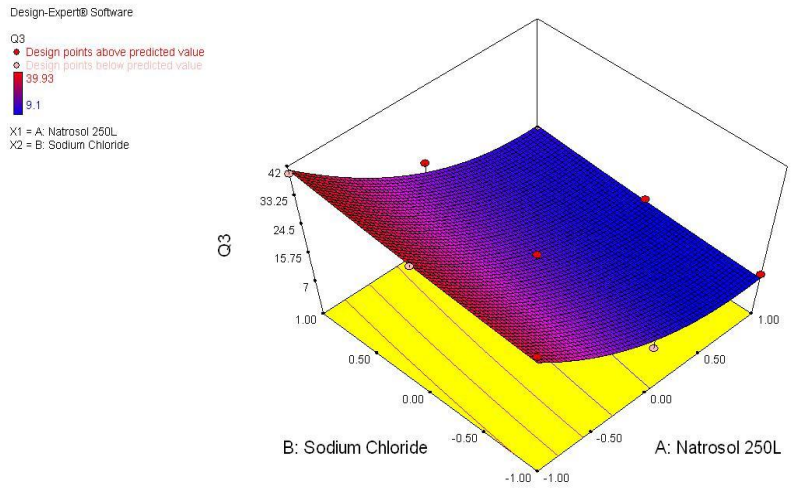

Fig. 9: Response surface plot of Q_3

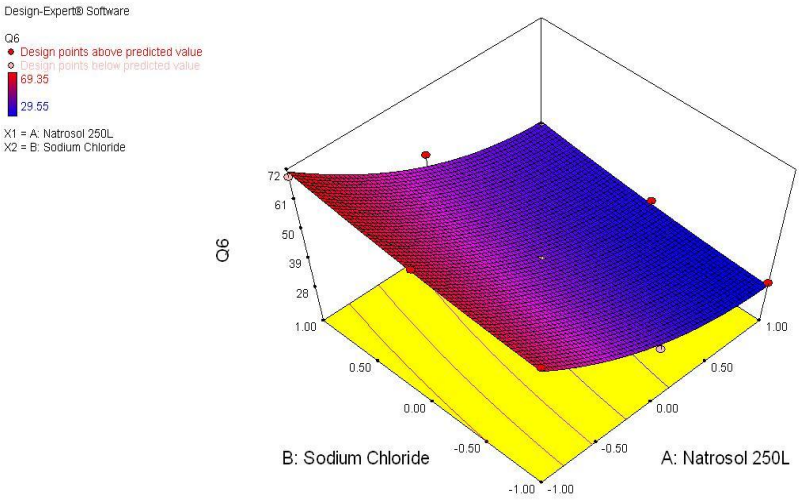

Fig. 10: Response surface plot of Q_6

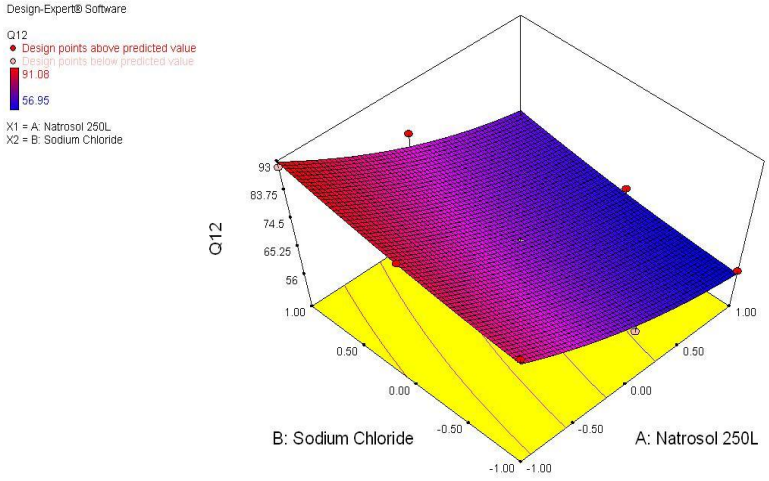

Fig. 11: Response surface plot of Q_{12}

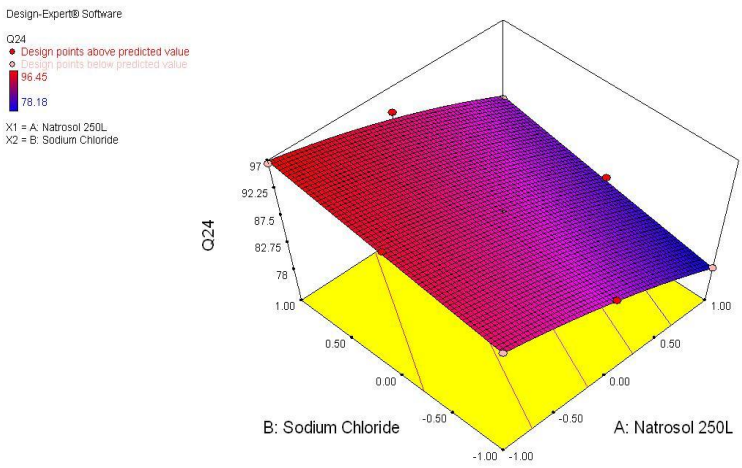

Fig. 12: Response surface plot of Q_{24}

Optimization (Model Validation)

The two formulations MVF1 and MVF2 were formulated for the model validation. The tablet properties were evaluated and found within limits (Table 9, 10). The close resemblance between predicted and observed response values indicates the validity of the generated model (Table 11).

Table 9: Core tablet properties evaluation.

Formulation Code	Thickness (mm)	Hardness (Kg/ cm^2)	Friability (%)	Drug Content (%)
MVF1	5.463 ± 0.012	7.830 ± 0.018	0.157 ± 0.012	99.478 ± 0.024
MVF2	5.489 ± 0.027	7.586 ± 0.024	0.148 ± 0.015	99.589 ± 0.048

All reading taken in triplicate, n ± SD

Table 10: Coated tablet properties evaluation of formulations MVF1 and MVF2.

Formulation Code	Average Weight (mg)	Thickness (mm)	Diameter (mm)
MVF1	375.667 ± 0.011	5.793 ± 0.023	9.698 ± 0.012
MVF2	376.667 ± 0.012	5.796 ± 0.025	9.745 ± 0.019

All reading taken in triplicate, n ± SD

Table 11: Comparison of predicted and experimental values of MVF1 and MVF2.

Responses	MVF1		MVF2	
	Predicted	Experimental	Predicted	Experimental
Q_3 (%)	35.00	37.30	15.56	14.92
Q_6 (%)	63.13	65.98	40.76	38.65
Q_{12} (%)	84.46	86.88	68.83	66.98
Q_{24} (%)	94.03	95.40	89.14	87.85

Grid Analysis

The grid analysis was performed for selection of the optimized level for Q_3, Q_6 Q_{12} and Q_{24}. The best results for Q_3, Q_6, Q_{12} and Q_{24} was obtained at the middle level concentration of % Natrosol 250L (8% w/w) and upper level concentration of % sodium chloride (18% w/w) in core tablet which revealed the release profile (Q_3, Q_6, Q_{12} and Q_{24}) as per the USP acceptance criteria (Table 12-15). The formulation F6 was selected as optimized formulation.

Table 12: Search for optimized level for Q_3.

Q_3											
O / R	**-1**	**-0.8**	**-0.6**	**-0.4**	**-0.2**	**0**	**0.2**	**0.4**	**0.6**	**0.8**	**1**
-1	35.06	29.47	24.52	20.21	16.53	13.50	11.11	9.35	8.23	7.76	7.92
-0.8	35.51	29.90	24.93	20.59	16.90	13.84	11.43	9.65	8.52	8.02	8.16
-0.6	35.99	30.36	25.37	21.01	17.30	14.22	11.79	9.99	8.83	8.31	8.44
-0.4	36.51	30.85	25.84	21.47	17.73	14.64	12.18	10.36	9.18	8.64	8.74
-0.2	37.06	31.38	26.35	21.95	18.20	15.08	12.60	10.76	9.57	9.01	9.08
0	37.64	31.95	26.89	22.47	18.70	15.56	13.06	11.20	9.98	9.40	9.46
0.2	38.26	32.54	27.47	23.03	19.23	16.07	13.55	11.67	10.43	9.83	9.87
0.4	38.91	33.17	28.07	23.62	19.80	16.62	14.08	12.18	10.92	10.29	10.31
0.6	39.59	33.83	28.72	24.24	20.40	17.20	14.64	12.72	11.43	10.79	10.79
0.8	40.31	34.53	29.39	24.89	21.03	17.81	15.23	13.29	11.99	11.32	11.30
1	41.06	35.26	30.10	25.58	21.70	**18.46**	15.86	13.89	12.57	11.89	11.84

O: Osmogen (Sodium chloride), R: Rate controlling polymer (Natrosol 250L)

Table 13: Search for optimized level for Q_6.

Q_6											
O / R	**-1**	**-0.8**	**-0.6**	**-0.4**	**-0.2**	**0**	**0.2**	**0.4**	**0.6**	**0.8**	**1**
-1	70.02	56.71	51.04	46.00	41.60	37.84	34.71	32.22	30.36	29.14	28.56
-0.8	70.46	57.14	51.47	46.43	42.02	38.25	35.12	32.62	30.76	29.54	28.95
-0.6	70.98	57.66	51.98	46.93	42.52	38.75	35.61	33.11	31.25	30.02	29.42
-0.4	71.59	58.26	52.58	47.53	43.11	39.34	36.19	33.69	31.82	30.58	29.98
-0.2	72.28	58.95	53.26	48.21	43.79	40.00	36.86	34.35	32.47	31.23	30.63
0	73.06	59.73	54.03	48.97	44.55	40.76	37.61	35.09	33.21	31.97	31.36
0.2	73.92	60.59	54.89	49.82	45.39	41.60	38.44	35.92	34.04	32.79	32.18
0.4	74.88	61.53	55.83	50.76	46.32	42.53	39.37	36.84	34.95	33.70	33.08
0.6	75.91	62.56	56.85	51.78	47.34	43.54	40.37	37.84	35.95	34.69	34.07
0.8	77.03	63.68	57.97	52.89	48.44	44.64	41.47	38.93	37.03	35.77	35.14
1	78.24	64.88	59.16	54.08	49.63	**45.82**	42.64	40.10	38.20	36.93	36.30

O: Osmogen (Sodium chloride), R: Rate controlling polymer (Natrosol 250L)

Table 14: Search for optimized level for Q_{12}.

Q_{12}											
O / R	**-1**	**-0.8**	**-0.6**	**-0.4**	**-0.2**	**0**	**0.2**	**0.4**	**0.6**	**0.8**	**1**
-1	82.41	78.38	74.67	71.26	68.17	65.39	62.92	60.77	58.92	57.39	56.17
-0.8	83.01	78.96	75.23	71.80	68.69	65.89	63.40	61.22	59.36	57.81	56.57
-0.6	83.71	79.64	75.88	72.44	69.30	66.48	63.97	61.78	59.89	58.32	57.06
-0.4	84.50	80.41	76.63	73.17	70.01	67.17	64.64	62.43	60.52	58.93	57.65
-0.2	85.39	81.28	77.48	73.99	70.82	67.96	65.41	63.17	61.25	59.63	58.33
0	86.37	82.24	78.42	74.92	71.72	68.84	66.27	64.01	62.07	60.43	59.11
0.2	87.45	83.30	79.46	75.93	72.72	69.82	67.23	64.95	62.98	61.33	59.99
0.4	88.63	84.46	80.60	77.05	73.81	70.89	68.28	65.98	64.00	62.32	60.96
0.6	89.90	85.71	81.83	78.26	75.01	72.06	69.43	67.11	65.10	63.41	62.03
0.8	91.27	87.05	83.15	79.57	76.29	73.33	70.68	68.34	66.31	64.59	63.19
1	92.73	88.50	84.58	80.97	77.67	**74.69**	72.02	69.66	67.61	65.87	64.45

O: Osmogen (Sodium chloride), R: Rate controlling polymer (Natrosol 250L)

Table 15: Search for optimized level for Q_{24}.

Q_{24}											
O / R	**-1**	**-0.8**	**-0.6**	**-0.4**	**-0.2**	**0**	**0.2**	**0.4**	**0.6**	**0.8**	**1**
-1	92.02	91.05	89.99	88.84	87.60	86.27	84.84	83.32	81.71	80.01	78.22
-0.8	92.49	91.54	90.50	89.37	88.15	86.84	85.43	83.93	82.34	80.66	78.88
-0.6	92.96	92.04	91.02	89.91	88.70	87.41	86.02	84.54	82.97	81.30	79.55
-0.4	93.45	92.54	91.54	90.44	89.26	87.98	86.61	85.15	83.60	81.96	80.22
-0.2	93.93	93.04	92.06	90.99	89.82	88.56	87.22	85.77	84.24	82.62	80.90
0	94.42	93.55	92.59	91.53	90.39	89.15	87.82	86.40	84.88	83.28	81.58
0.2	94.91	94.06	93.12	92.09	90.96	89.74	88.43	87.03	85.53	83.95	82.27
0.4	95.41	94.58	93.66	92.64	91.53	90.34	89.04	87.66	86.18	84.62	82.96
0.6	95.92	95.10	94.20	93.20	92.12	90.93	89.66	88.30	86.84	85.29	83.65
0.8	96.43	95.63	94.75	93.77	92.70	91.54	90.29	88.94	87.50	85.97	84.35
1	96.94	96.16	95.30	94.34	93.29	**92.15**	90.91	89.59	88.17	86.66	85.06

O: Osmogen (Sodium chloride), R: Rate controlling polymer (Natrosol 250L)

Effect of pH on Drug Release

The effect of pH on drug release for the optimized formulation (F6) was studied by performing dissolution studies in 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer for 24 h. The system was independent of the pH since no significance in drug release was observed (Fig. 13). This was an important performance test because, if the semi permeable membrane was truly selective, diffusion of ions into the osmotic pump would be negligible which should affect the release profiles. In other words, the osmotic tablets exhibited media independent release. Thus, the fluid in different parts of GI tract will scarcely affect drug release from the osmotic system.

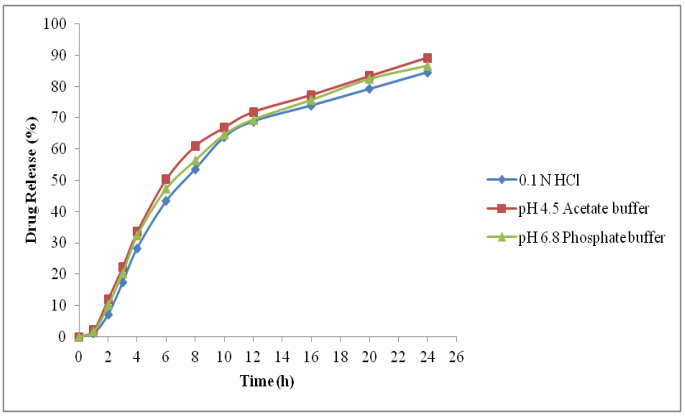

Fig. 13: Effect of pH on drug release.

Effect of Agitation Intensity on Drug Release

To study the effect of agitation intensity, optimized formulation (F6) was subjected to dissolution in deionized water at 50, 100 and 150 rpm. There was no significant difference in the release profile of the system with change in agitation intensity (Fig. 14).

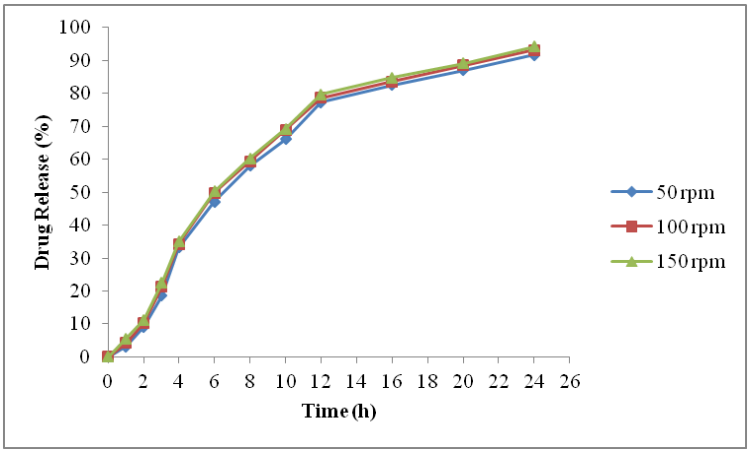

Fig. 14: Effect of agitation intensity on drug release.

Effect of Orifice Diameter on Drug Release

The effect of orifice diameter was studied on coated tablets of optimized formulation (F6) were mechanically drilled on one side with 0.4 mm, 0.6 mm and 0.8 mm drill.

The drug release increased, while lag time decreased with an increase in orifice diameter from 0.4 mm to 0.8 mm, respectively (Fig. 15). The orifice diameter 0.6 mm showed promising results to achieve desired drug release from the SCOP.

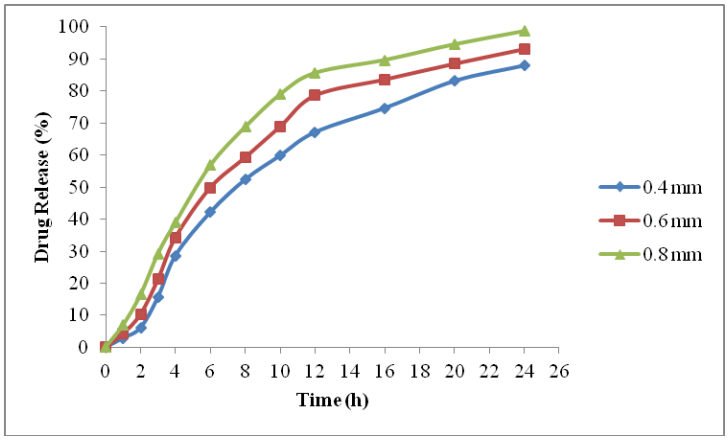

Fig. 15: Effect of orifice diameter on drug release.

Surface Morphology Study

To evaluate the surface morphology of the coating membrane, surfaces of the optimized formulation (F6) were examined using scanning electron microscopy (SEM) both before and after dissolution (JEOL JSM 6380) (Fig. 16). Membranes were dried at 45ºC for 12 hours and stored between sheets of wax paper in a dessicator until examination.

Fig. 16(a) shows membrane structure before dissolution, initially the surface of coated tablets was smooth before coming into contact with aqueous environment and coats appeared to be free of pores. A microporous structure of the membrane after dissolution was observed from Fig. 16(b) which shows SEM of membrane after dissolution. The significant porosity has resulted due to leaching of water-soluble additive i.e. PEG 8000 during dissolution.

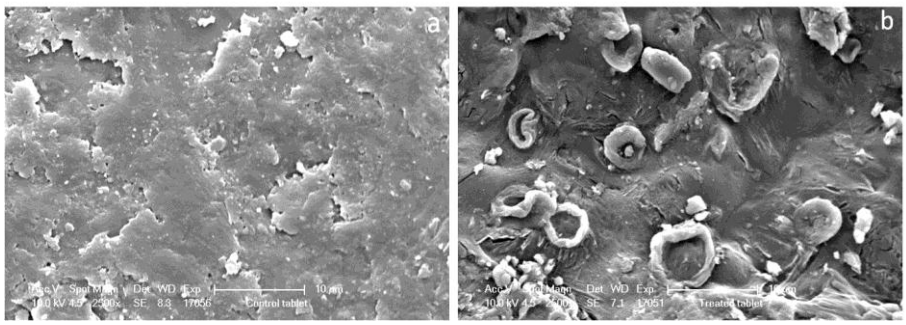

Fig. 16: SEM microphotographs of SCOP tablet at 2500x (a) before dissolution, (b) after dissolution.

Stability Study

The optimized formulation (F6) was packed in aluminium foil and subjected to stability studies as per ICH guidelines, 40°C ± 2°C/75% RH ± 5% RH (Thermolab). Samples were

withdrawn at time intervals of 1, 2 and 3 month. The samples were evaluated for appearance, assay and *in vitro* release profile (Table 16).

Table 16: Stability study.

Tests	Limits	Initial	1 Month	2 Months	3 Months
Appearance	White to off white	Complies	Complies	Complies	Complies
Assay (%)	Carbamazepine USP (NLT 90% to NMT 110% of labeled amount of Carbamazepine)	101.20	99.63	100.60	100.18
Drug Release (%)	3h =10 to 35 9h =35 to 65 12h =65 to 90 24 h =NLT 75	21.24 49.89 78.66 93.12	21.18 49.75 78.52 93.10	20.95 48.91 77.96 92.98	21.15 49.50 77.92 92.94

CONCLUSION

The solubility of poorly water soluble CBZ is enhanced through the incorporation of optimized concentration of PVP K30 and SLS in the core tablet. The statistical approach for formulation optimization is a useful tool, particularly when two or more variables are to be evaluated simultaneously. A 3^2 factorial design was performed, and the desired release of CBZ from the SCOP was achieved through careful monitoring of the selected formulation variables. The variables Hydroxyethyl cellulose i.e. Natrosol 250L (%) and osmogen i.e. sodium chloride (%) in core tablet evaluated in the study exhibited significant effect on the responses Q_3, Q_6, Q_{12} and Q_{24} of the formulations. It was evident that an increase in % of osmogen (sodium chloride) resulted in an increase in the drug release. The increase in % of rate controlling polymer (Natrosol 250L) in the core tablet showed decrease in drug release. Increase in concentration of pore former the drug release was found to be increased. The results revealed that with an increase in the %weight gain the consistency of coat improved but the drug release decreased. The grid analysis was performed for the selection of optimized level for release profile (Q_3, Q_6, Q_{12} and Q_{24}) revealed F6 as the optimized formulation. The best results for Q_3, Q_6, Q_{12} and Q_{24} was obtained at the middle level concentration of % Natrosol 250L (8% w/w) and upper level concentration of % sodium chloride (18% w/w) in core tablet showed the release profile (Q_3, Q_6, Q_{12} and Q_{24}) as per the USP acceptance criteria. Hydroxyethyl cellulose (Natrosol 250L) with drug particles forms a viscous suspension and prevents settling of drug particles inside the core tablet and ensured the drug is release at a relatively constant rate. The optimized formulation (F6) delivered CBZ independent of pH and agitation intensity and was found to be stable. The orifice

diameter is one of the critical parameter that greatly influences release rate and 0.6 mm is selected as optimized diameter to achieve desired drug release from the SCOP. Overall, a controlled release SCOP system for CBZ has been successfully developed using the 3^2 factorial design. Finally, it is concluded that release of CBZ is significantly controlled for 24 h from the single core osmotic pump tablet and thus it is a promising approach for the better management of partial and tonic-clonic seizures.

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